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GUIDELINES

Guidelines on optimizing the use of proton pump inhibitors: PPI stewardship

Amit Kumar Dutta[1] · Abhinav Jain[2] · Vaneet Jearth[3] · Ramit Mahajan[4] · Manas Kumar Panigrahi[5] · Vishal Sharma[3] · Mahesh Kumar Goenka[6] · Rakesh Kochhar[7] · Govind Makharia[8] · Duvvur Nageshwar Reddy[9] · Richard Kirubakaran[10] · Vineet Ahuja[8] · Neha Berry[11] · Naresh Bhat[12] · Usha Dutta[3] · Uday Chand Ghoshal[13] · Ajay Jain[14] · Umesh Jalihal[15] · V. Jayanthi[16] · Ajay Kumar[17] · Sandeep Nijhawan[18] · Ujjal Poddar[13] · G. N. Ramesh[19] · Shivram P Singh[20] · Showkat Zargar[21] · Shobna Bhatia[22]

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Abstract

Proton pump inhibitors (PPIs) have been available for over three decades and are among the most commonly prescribed medications. They are effective in treating a variety of gastric acid-related disorders. They are freely available and based on current evidence, use of PPIs for inappropriate indications and duration appears to be common. Over the years, concerns have been raised on the safety of PPIs as they have been associated with several adverse effects. Hence, there is a need for PPI stewardship to promote the use of PPIs for appropriate indication and duration. With this objective, the Indian Society of Gastroenterology has formulated guidelines on the rational use of PPIs. The guidelines were developed using a modified Delphi process. This paper presents these guidelines in detail, including the statements, review of literature, level of evidence and recommendations. This would help the clinicians in optimizing the use of PPIs in their practice and promote PPI stewardship.

Keywords Adverse effects · Contraindications · Duration · Inappropriate use · Indications · Proton pump inhibitors · Stewardship

Introduction

Proton pump inhibitors (PPIs) are among the most commonly prescribed medications in clinical practice. They are used for a variety of indications and have been very effective in the management of several conditions such as peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD). They are generally safe when used for short term,

✉ Amit Kumar Dutta
akdutta1995@yahoo.co.in

1 Department of Gastroenterology, Christian Medical College and Hospital, Vellore 632 004, India

2 Gastro 1 Hospital, Ahmedabad 380 060, India

3 Postgraduate Institute of Medical Education and Research, Chandigarh 160 012, India

4 Dayanand Medical College and Hospital, Ludhiana 141 001, India

5 All India Institute of Medical Sciences, Bhubaneswar 751 019, India

6 Apollo Hospital, Kolkata 700 054, India

7 Paras Hospitals, Panchkula 134 109, India

8 All India Institute of Medical Sciences, New Delhi 110 029, India

9 AIG Hospitals, Hyderabad 500 032, India

10 Center of Biostatistics and Evidence Based Medicine, Vellore 632 004, India

11 BLK Institute of Digestive and Liver Disease, New Delhi 201 012, India

12 Aster CMI Hospital, Bengaluru 560 092, India

13 Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow 226 014, India

14 Choithram Hospital and Research Center, Indore 452 014, India

15 Karnataka Gastro Center, Bengaluru 560 086, India

16 Sri Ramachandra Medical College, Chennai 600 116, India

17 Institute of Digestive and Liver Diseases, BLK - Max Superspeciality Hospital, New Delhi 201 012, India

18 Sawai Man Singh Medical College, Jaipur 302 004, India

19 Aster Medcity, Kochi 682 027, India

20 Kalinga Gastroenterology Foundation, Cuttack 753 001, India

21 Department of Gastroenterology, Sher-i-Kashmir Institute of Medical Sciences, Kashmir 190 011, India

22 Sir H N Reliance Foundation Hospital, Mumbai 400 004, India

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but long-term use has been associated with various adverse effects. PPIs are freely available in India and apart from use for direct indications, they are also co-prescribed with other medications for various reasons, including prevention of adverse effects. Considering their widespread use and the potential of adverse effects as well as cost of therapy, when used for long term and for unclear indications, there is a need for PPI stewardship. This includes both preventing inappropriate use and promoting appropriate use when required. The Indian Society of Gastroenterology (ISG) was tasked with the formulation of guidelines on the rational use of PPIs. This paper presents these guidelines in detail, including the level of evidence and strength of recommendation.

Proton pump inhibitors: General considerations

Gastric acid has long been known to be a major contributing factor in various upper gastrointestinal illnesses. Nearly three decades of targeted efforts lead to the launch of the first proton pump inhibitor, omeprazole, in 1988 [1]. Several other PPIs were introduced subsequently—pantoprazole, lansoprazole, esomeprazole, rabeprazole, ilaprazole and dexlansoprazole. The availability of PPI changed the landscape of management of acid-related gastrointestinal disorders.

PPIs are benzimidazole derivatives, membrane permeable and acid labile weak bases [2]. To prevent inactivation by gastric juice, these are delivered via enteric-coated tablets or gelatin capsules containing enteric-coated granules. Parenteral formulations are also available and are well-suited for patients in whom the oral route of administration is not appropriate.

PPIs are weak bases that accumulate selectively in the acidic space of the secretory canaliculus of gastric parietal cells after absorption from the small intestine. They are a prodrug and undergo acid-catalyzed cleavage of a chiral sulfoxide bond into active sulfenic acid and/or sulfonamide. These compounds then bind covalently to cysteine residues on the H+/K+ ATPase and act to inhibit acid secretion until replacement pumps can be synthesized which may take up to 36 hours [2]. PPI require active canalicular expression of H+/K+ ATPases for binding, which occurs in response to a meal. Hence, a PPI is taken half an hour before the meal to ensure adequate concentration of the drug in the canaliculus before increased expression of H+/K+ ATPases that occurs in response to a meal [2].

PPIs are metabolized by the hepatic P450 cytochromes [3]. CYP2C19 and CYP3A4 are the main cytochromes metabolizing PPIs. Omeprazole and pantoprazole are metabolized almost entirely by CYP2C19, while S enantiomer of omeprazole (esomeprazole) has lower affinity for this enzyme. Rabeprazole and lansoprazole are metabolized by both CYP2C19 and CYP3A4 [3]. Drug interactions appear less significant with these agents, perhaps owing to this difference. Following hepatic metabolism, the ultimate excretion of most benzimidazoles is renal, though lansoprazole/dexlansoprazole are also excreted via the biliary canaliculi [3]. There is potential for interactions with drugs sharing the same metabolic pathway and several drug interactions have been associated with PPI use. For example, PPI and clopidogrel are metabolized by the same CYP2C19. Ex-vivo analyses showed that omeprazole influences the antiplatelet effects of clopidogrel. However, no significant harmful effect of omeprazole on the efficacy of clopidogrel has been demonstrated in prospective studies [4]. By suppressing gastric acid, PPIs can alter the absorption of various drugs. For example, absorption of L-thyroxine, itraconazole, cefpodoxime, atazanavir and dipyridamole is decreased, whereas the absorption of nifedipine and digoxin is increased with the concomitant use of PPIs [4].

With regard to the efficacy of various PPIs, differences in their pharmacological properties have generally not been shown to have a significant impact on efficacy and any PPI may be used for acid suppression. The standard dose of PPI is as follows: pantoprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, esomeprazole 40 mg and rabeprazole 20 mg [5]. The potency of PPI is generally compared with omeprazole (first available PPI) and expressed as omeprazole equivalent (OE). The estimated OE for various PPIs is as follows: pantoprazole 40 mg (9 mg OE), esomeprazole 40 mg (64 mg OE), rabeprazole 20 mg (36 mg OE) and lansoprazole 30 mg (27 mg OE) [6]. Vonoprazan, a novel oral potassium-competitive acid blocker, inhibits gastric H+, K+-ATPase, [7]. However, unlike PPIs, vonoprazan inhibits the enzyme in a K+-competitive and reversible manner. It has a rapid onset of action within six hours with no relation to intake of food. It is considered to have higher potency than PPI for acid suppression. This drug is currently not available in India.

Guideline formulation process

The process of formulating the guidelines was initiated in June 2022. We followed the modified Delphi process for developing the guidelines [8]. To have a wider representation in the membership of guideline drafting committee, members were selected in such a way that there was representation from (i) different parts of the country, (ii) academic and non-academic centers and (iii) public and private organizations.

The core group met on a virtual platform to decide on the scope of the guidelines, topics to be covered, statement generation and the methods to be followed. The statements were generated and the relevant literature was searched for each of the statements. The literature search was done in the PubMed as well as Cochrane database

from inception up to July 2022. The searched literature was made available to all members via Google Drive. The members were divided into three groups and each group was allotted a set of statements for discussion and modification as per requirement. The groups discussed the statements, modified these and added more statements as required. Once the three groups completed their meetings, all statements were collated together and opened for the first round of voting by all members using Google forms. There were five choices for voting—(i) Strongly agree, (ii) Agree, (iii) Uncertain, (iv) Disagree and (v) Strongly disagree. For a statement to be accepted, at least 80% of the members had to agree (strongly agree or agree). The members were also invited to add comments for each of the statements. After first round of online voting, statements where agreement could not be reached were modified based on the comments and suggestions and put to vote again via Google forms. The results and comments were recorded.

Following the two rounds of online voting, an in-person meeting was held for discussion and final round of voting in New Delhi on October 8 and 9, 2022. During this meeting, each statement along with relevant literature, level of evidence, results of online voting and comments/suggestions made during online voting was presented. This was followed by discussion among members. The statements were modified, if required, before voting. Voting was done for agreement and strength of recommendation. The levels of evidence and strength of recommendations were made according to the GRADE process (Table 1) [9, 10]. The factors included in deciding on the level of evidence included the study design, indirectness, imprecision, risk of bias, inconsistency, effect size and other considerations. An expert in evidence-based medicine and systematic review was included in the group for the application of GRADE process and was assisted by the core committee members. Statements where evidence was not feasible/applicable were considered good clinical practice statements. The recommendation (strong or conditional) was made by the members together after assessing quality of evidence, balance between desirable and undesirable effects, cost and patients' values and preferences. Table 2 provides the list of all statements, result of voting on agreement, level of evidence and strength of recommendation (where applicable).

Optimizing the use of PPI

Statement 1A: Inappropriate use of PPIs is quite common in clinical practice.

Level of evidence - moderate

Statement 1B: PPIs should be discontinued if there is no definite indication.

Good clinical practice statement; strong recommendation

There are four potential scenarios of inappropriate use of PPIs: (i) for inappropriate indication, (ii) for longer than the recommended duration, (iii) at a higher than the recommended dose and (iv) failure to use PPIs when it is clinically indicated. A number of studies published over the last two decades have shown inappropriate use in a significant proportion of patients [11–14]. These range from information obtained from large databases, retrospective study and prospective and cross-sectional studies. The evaluations of large databases from the US, France and Switzerland have shown the use of PPIs for inappropriate indication and higher than recommended cumulative dosing to be up to 60% [13–15]. While databases provide large datasets, these, however, may lead to bias because of a lack of detailed clinical review of patient's medical records.

There are many studies across the globe that have reported inappropriate use of PPIs based on the detailed evaluation of patient records and direct information from patients. These differ in terms of study design, population

Table 1 Level of evidence and strength or recommendation

Level of evidence	
High	Very confident that the true effect lies very close to the estimate of effect.
Moderate	Moderate confidence in the estimate of effect: The true effect is likely to be close to the estimated effect, but it may be substantially different.
Low	Limited confidence in the effect of estimate: The true effect may be substantially different.
Very low	Very low confidence in the effect of estimate: The true effect is likely to be substantially different from the estimated effect.
Strength of recommendation	
Strong	The intervention is recommended in most individuals.
Conditional	The choice would vary between individuals and decision should include clinical situation and patients' values and preferences.

Source: Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations. Updated October 2013. The GRADE Working Group, 2013. Available from guidelinedevelopment.org/handbook

Table 2 List of statements with level of evidence and strength of recommendations

Statement	Strongly agree or agree	Level of evidence	Strength of recommendation
Optimizing use of proton pump inhibitors			
Statement 1A: Inappropriate use of PPIs is quite common in clinical practice.	100%	Moderate	—
Statement 1B: PPI should be discontinued if there is no definite indication.	100%	GPS	Strong
Statement 2: For deprescribing PPIs, strategy of both dose tapering and abrupt discontinuation has shown similar results. The strategy needs to be individualized and flexible.	94.5%	Low	Conditional
Indications for PPIs			
Statement 3: For patients with mild erosive esophagitis, NERD or uninvestigated gastroesophageal reflux symptoms, a standard dose of PPI is recommended for a maximum period of 8 weeks.	88.9%	High	Strong
Statement 4A: In patients with severe erosive esophagitis or peptic stricture, initial treatment should be with double dose of PPIs for at least 8 weeks.	100%	Moderate	Strong
Statement4B. Patients with severe erosive esophagitis or peptic stricture require a long-term maintenance therapy with PPIs.	100%	Moderate	Strong
Statement 4C: Patients with Barrett's esophagus require long-term maintenance therapy with PPIs.	100%	Low	Conditional
Statement 5: For patients with NERD or mild GERD, if maintenance PPI is required, on-demand therapy is recommended.	88.9%	Moderate	Strong
Statement 6A: For patients having non-cardiac chest pain or extraesophageal symptoms of GERD, a PPI trial of up to 8 weeks can be instituted.	95.2%	Low*	Conditional
Statement 6B: Patients not responding to therapeutic trial of PPIs require objective evaluation for the diagnosis of GERD.	84.2%	GPS	Strong
Statement 7A: In patients with uninvestigated dyspepsia, without alarm symptoms, a standard-dose PPI should be used for 2 to 4 weeks as an initial therapy.	100%	Moderate	Strong
Statement 7B: In patients with functional dyspepsia, standard-dose PPIs should be used for 2 to 4 weeks as an initial therapy.	95%	Moderate	Strong
Statement 7C: In patients with uninvestigated dyspepsia without alarm features, prolonged or continuous use of PPIs is not recommended.	100%	GPS	Strong
Statement 8: Standard-dose PPIs in twice daily doses is an essential component of drug therapy for the eradication for *H. pylori*.	100%	High	Strong
Statement 9: In patients with peptic ulcer disease, after H. pylori eradication therapy, PPIs in standard dose should be given for additional 2 weeks for duodenal ulcer and at least 4 weeks for gastric ulcer.	100%	Moderate	Strong
Statement 10: After successful endoscopic therapy for bleeding peptic ulcer, high-dose PPI is recommended for 72 h.	100%	High	Strong
Statement 11: In patients with eosinophilic esophagitis, PPIs, dietary modification and topical glucocorticoid alone or in combination may be used as the first-line therapy.	100%	Moderate	Strong
PPI prophylaxis			
Statement 12: Standard-dose PPI prophylaxis may be introduced in patients receiving single antiplatelet drug in the presence of additional risk factors or in those on dual antiplatelet drugs.	100%	Moderate	Strong
Statement 13: For patients on anticoagulants, standard-dose PPI prophylaxis is recommended only if there are additional risk factors.	100%	Low	Strong
Statement 14: In patients on short or long-term corticosteroids, routine PPI prophylaxis is not recommended.	100%	Low	Strong
Statement 15A: Routine PPI prophylaxis is not recommended for all patients on non-steroidal anti-inflammatory drugs.	100%	Moderate	Strong
Statement 15B: In patient taking NSAID, use of PPI is recommended based on the risk assessment for the prevention of GI complications.	100%	GPS	Strong
Statement 16: In critically ill patients, prophylaxis with standard-dose PPI is recommended only in the presence of risk factors for gastrointestinal bleeding.	100%	Moderate	Strong
Statement 17: Standard-dose PPI may be considered for short duration after endoscopic variceal ligation.	57.9%	Low	Statement not accepted

Table 2 (continued)

Statement	Strongly agree or agree	Level of evidence	Strength of recommendation
PPI in special situations			
Statement 18: If indicated, PPIs in standard dose can be used in patients with chronic kidney disease.	100%	Very low	Strong
Statement 19: In patients with cirrhosis of liver, PPIs should be used with caution.	100%	Very low	Strong
Statement 20: In patients receiving pancreatic enzyme therapy, routine use of PPIs is not recommended.	100%	Low	Strong
Statement 21A: PPIs are indicated in children over 1 year of age for a short-term for the treatment of symptomatic GERD, healing of erosive esophagitis, peptic ulcer disease and *H. pylori* eradication.	100%	Low	Strong
Statement 21B: Use of PPIs should be discouraged in children below 1 year of age.	100%	GPS	Strong
Statement 22A: A standard-dose PPI, if indicated, may be used in pregnant women in their second or third trimester of pregnancy.	100%	Low	Strong
Statement 22B: The use of PPIs should be avoided, unless there is a strong indication, during the first trimester of pregnancy.	100%	GPS	Strong
Co-prescription of PPI with other drugs			
Statement 23A: Routine addition of prokinetic to PPIs is not indicated in patients with GERD.	94.4%	Moderate	Strong
Statement 23B: Routine use of fixed dose combination therapy of PPIs and prokinetics should be avoided.	100%	GPS	Strong
Statement 24: There is no need to co-prescribe PPIs routinely in patients in whom antibiotics are prescribed.	100%	Low	Strong
Statement 25: There is no rationale for co-prescribing PPIs with probiotics routinely.	94.4%	Moderate	Strong
Statement 26: There is no indication for adding PPIs to SSRI routinely.	84.2%	Low	Strong
Statement 27: PPIs should not be routinely added while prescribing bisphosphonate.	100%	Low	Strong
Adverse effects of PPI			
Statement 28: Use of PPIs is associated with an increased risk of certain gastrointestinal infections.	100%	Low	-
Statement 29: Use of PPIs is associated with an increase in the risk of acute interstitial nephritis.	100%	Low	-
Statement 30: There is uncertainty about the increased risk of bone fracture with use of PPIs.	94.7%	Very low	-
Statement 31 A: Use of PPIs is associated with an increased risk of hypomagnesemia.	84.2%	Low	-
Statement 31B: Long-term use of PPIs is associated with a small increase in the risk of vitamin B_{12} and iron deficiency	84.2%	Low**	-

*The level of evidence for non-cardia chest pain was moderate and for extraesophageal symptoms was low

**The level of evidence was low for vitamin B_{12} deficiency and very low for iron deficiency

GERD gastroesophageal reflux disease, *GI* gastrointestinal, *GPS* good clinical practice statements, *NERD* non-erosive reflux disease, *NSAID* nonsteroidal anti-inflammatory drug, *PPI* proton pump inhibitors, *SSRI* selective serotonin reuptake inhibitor

they evaluated (adults, children, elderly, mixed group), patient profile (outpatients, inpatients) or setting of PPI use (general or specific situation such as stress ulcer prophylaxis) [11, 12, 16–18]. Irrespective of the study design and patient groups evaluated, the use of PPIs without proper indications ranges from 20% to 90% and exceeds 40% in a majority of them [11, 17–19]. A prospective study from the southern part of India showed lack of proper indication for the use of PPIs in 57% of the prescriptions [19]. The rate of inappropriate use was even higher (86.2%) in another Indian study, including pediatric population and most often these were co-prescribed with steroids or non-steroidal anti-inflammatory drugs (NSAIDs) [20]. Overall, there is significant overuse of PPIs and there is an urgent need for PPI stewardship. This would help to reduce the adverse effects, drug interactions, pill burden and the cost of the therapy.

Statement 2: For deprescribing PPIs, strategy of both dose tapering and abrupt discontinuation has shown similar results. The strategy needs to be individualized and flexible.

Level of evidence - low; conditional recommendation

Studies evaluating step-down therapy vs. continuous therapy and abrupt discontinuation vs, continuous therapy of PPIs have reported a success rate of discontinuation of PPIs ranging from 30% to 80% (Table 3) [21–24]. The efficacy of step-down therapy appears better than that of abrupt discontinuation in deprescribing PPIs, but these studies lack direct comparison between the two strategies. There is only one published randomized controlled trial (RCT) comparing two methods (abrupt discontinuation vs. slow tapering) of discontinuing PPIs. PPIs were tapered over three weeks in the slow tapering group [25]. It showed no significant difference between the two study arms on the likelihood of remaining off PPIs and being symptom-free at six months, i.e. 31% vs. 22% for tapered vs. abrupt discontinuation (Table 3) [25]. Thus, currently, both tapering or abrupt discontinuation seem reasonable alternatives. The recent American Gastroenterological Association practice update on deprescribing of PPIs also suggested the same [26]. However, there is some concern about rebound acid hypersecretion after abrupt discontinuation of PPIs and as robust evidence on deprescribing method is lacking, an individualized approach may be appropriate.

Indications for the use of PPIs

Gastroesophageal reflux disease

GERD is defined as reflux of gastric content into the esophagus, which leads to symptoms/complications [27]. It is common with an estimated worldwide prevalence of around 15% [28]. A systematic review estimated the pooled prevalence of GERD in Indian population to be 15.6% (95% CI 11.1–20.7) [29]. It is frequent in both urban and rural Indian population [30]. Accordingly,

Table 3 Studies on different deprescribing protocols for proton pump inhibitors

Reference	Study design	Participants and indication	PPI duration	PPI dose	Deprescribing method	Follow-up	Outcome	Comment
Step-down studies								
Inadomi et al. (2003, [22])	Non-controlled prospective study	*n*=117 M:F 112/5 Heartburn	> 8 weeks	>20 mg	Step down from multiple to single dose	6 months	Step down was successful in 79.5%	Longer PPI duration before step down was an independent predictor of PPI requirement
Helgadottir et al. (2017, [21])	Double-blind randomized trial	*n*=50 M:F25/25 GERD with EE	>2 years	40/20 mg	Step-down vs. same dose	8 weeks	Step down was successful in 76%	Female gender was an independent predictor for successful step down
Abrupt discontinuation studies								
Pilotto et al. (2003, [23])	Double-blind randomized trial	*n*=56 Erosive esophagitis	>6 months	20 mg	Abrupt discontinuation vs. continuation treatment	1 year	62.5% had relapse of erosive esophagitis 6 months after discontinuation	81% healing rate in the maintenance phase after 4 months of 20 mg following a step down from 40 mg for 8 weeks
Bjornsson et al. (2006, [25])	Double-blind placebo-controlled trial	*n*=96 M:F - 44/52 Long-term PPI users without PUD or EE	>8 weeks	20 mg	Abrupt discontinuation vs. 3 week tapering	1 year	Discontinuation was successful in 27% (31% of tapering and 22% of abrupt discontinuation)	GERD and serum gastrin were independent predictors of PPI requirement
Van der Velden et al. (2010, [24])	Double-blind parallel group trial	*n*=141 GERD patients on long-term PPI therapy	> 6 months	20 mg	Abrupt discontinuation with 20 mg PPI escape vs. daily PPIs with placebo escape	13 weeks	38% persisted with daily PPIs, 43% reduced dosage, 25% used <2 tablets/week	About 20% long-term PPI users became satisfied with placebo with minimal PPI intake (<1 tablet/week)

EE eosinophilic esophagitis, *F* female, *GERD* gastroesophageal reflux disease, *M* male, *n* number of participants, *PPI* proton pump inhibitors

GERD is one of the common reasons for which acid suppressant drugs are prescribed. Patients without alarm symptoms do not need formal tests to establish the diagnosis of GERD and constitute a majority of cases seen in clinical practice (uninvestigated GERD). Patients with reflux symptoms who have a normal endoscopic examination are labeled as having non-erosive reflux disease (NERD), while those having erosions/ulcers are labeled as having erosive reflux disease (ERD), which is further graded based on the extent and severity of ulceration. The clinical manifestations and severity of symptoms vary and treatment must be tailored according to the phenotype of the disease. The efficacy of PPI therapy is better for healing of esophagitis and relief of heartburn, but is lower for regurgitation and extraesophageal symptoms [31, 32]. The ISG has recently published detailed guidelines on GERD and only select key issues related to the use of PPIs for the management of GERD are discussed here [27].

Statement 3: For patients with mild erosive esophagitis, NERD or uninvestigated gastroesophageal reflux symptoms, a standard dose of PPI is recommended for a maximum period of 8 weeks.

Level of evidence - high; strong recommendation

Acid suppression is the cornerstone of medical management of GERD. PPIs are preferred over histamine-2 receptor antagonists (H_2RAs) for acid suppression, as these are more effective in symptom relief (NERD, ERD) as well as for healing of esophagitis (ERD) [33, 34]. Prokinetics are inferior to PPIs and H_2RAs and are generally not recommended for initial therapy [34, 35]. A Cochrane review of 34 studies on patients with uninvestigated GERD and NERD confirmed the efficacy of standard-dose PPIs in relief of symptoms [34]. A majority of the studies used standard-dose PPIs once daily for four weeks, while a few used it for two or eight weeks. A therapy for four weeks appears appropriate and may be extended for eight weeks if there is no or partial response. Overall, the response to standard-dose PPI therapy is seen in 60% to 80% of cases [36]. A network meta-analysis, including 15 trials with over 6000 patients with NERD, showed superiority of different PPIs over placebo for symptom relief and there is little evidence to support the superiority of one PPI over another for initial symptom management [37]. In addition to acid suppression therapy, lifestyle measures to reduce reflux should be stressed upon.

The use of double dose PPIs is not recommended for initial therapy; in patients with no response to therapy after eight weeks, two RCTs have shown some benefit of adding double dose PPIs for further eight weeks [36, 38, 39]. There appears to be no benefit of increasing the dose of PPIs for the symptom of regurgitation [40, 41]. If symptoms persist, investigations for GERD should be done to confirm/exclude the diagnosis. Patients with heartburn but no objective evidence of GERD on 24-hour ambulatory pH study may be diagnosed as having functional heartburn. PPIs have no benefit in this group of patients except when there is an overlap of GERD with functional heartburn [42].

Statement 4A: In patients with severe erosive esophagitis or peptic stricture, initial treatment should be with double dose of PPIs for at least 8 weeks.

Level of evidence - moderate; strong recommendation

Statement 4B. Patients with severe erosive esophagitis or peptic stricture require a long-term maintenance therapy with PPIs.

Level of evidence - moderate; strong recommendation

Statement 4C: Patients with Barrett's esophagus require long-term maintenance therapy with PPIs.

Level of evidence - low; conditional recommendation

Erosive esophagitis is present in <30% of patients with symptoms of GERD [43]. Severe esophagitis generally refers to Los Angeles grade C or D lesions on endoscopy [35, 43]. PPIs lead to significantly better (>80%) and faster healing of erosive esophagitis compared to H_2RAs and thus, PPIs are the treatment of choice [33]. The healing effect of PPIs for erosive esophagitis increases progressively for up to eight weeks (>80% healing rate) and hence, eight weeks of therapy is recommended [33]. Using PPIs twice daily may improve the healing rate and the difference is more pronounced in patients having severe esophagitis [44]. Two meta-analyses showed esomeprazole to be slightly superior to other PPIs in healing esophagitis, but the added benefit was small and hence, for practical purposes, any PPI may be used [45, 46].

In patients with erosive esophagitis, the discontinuation of PPIs leads to relapse of symptoms and recurrence of endoscopic lesions in a majority of them [47]. A meta-analysis of 10 RCTs showed recurrence of erosive esophagitis in 78.8% of patients on placebo over a 12-month period [47]. When PPI therapy was continued, the recurrence rate was only 21.7%. Similar effects were noted on clinical symptoms: relapse of symptoms was noted in 76.3% on placebo vs. 29.4% on PPIs. The relapse of symptoms is more frequent in patients with severe esophagitis and hence, these patients require standard-dose maintenance PPIs for long term [35, 47, 48].

For peptic strictures of the esophagus, the use of long-term PPIs has been associated with a greater proportion of patients with sustained relief of symptoms and reduced requirement of endoscopic dilatation. Three RCTs have compared the efficacy of PPIs with H_2RAs for peptic esophageal strictures and they showed a greater symptomatic response with PPIs along with reduced need for repeat dilatation [49–51].

Long-term use of standard-dose PPIs may reduce the progression to high-grade dysplastic or neoplastic lesion in Barrett's esophagus [52, 53]. There are no RCTs on the

efficacy of PPIs and the evidence of benefit comes from observational studies. A systematic review of seven studies (five cohort studies, two case-control studies), which included 2813 patients, showed 71% reduction in progression to high-grade dysplasia and adenocarcinoma with the use of PPIs [52]. The benefit was more apparent after two to three years of taking PPIs. However, number needed to treat (NNT) ranged from 82 to 220. These studies have generally been done in the western population and their applicability in Asian patients needs to be evaluated.

Statement 5: For patients with NERD or mild GERD, if maintenance treatment with PPIs is required, on-demand therapy is recommended.

Level of evidence - moderate; strong recommendation

A majority of patients with GERD have recurrence of symptoms after stopping PPIs. The treatment options include continuous PPI therapy vs. on-demand therapy. A recent meta-analysis of 11 studies showed similar outcomes in the on-demand and continuous PPI group (OR of failure of therapy 1.26; 95% CI: 0.76–2.07) [54]. This was especially true for patients with NERD or mild erosive esophagitis [54]. There was a significant reduction in PPI use in the on-demand group. Similar findings were also noted in an earlier systematic review [55]. Hence, on-demand PPIs, i.e. patient takes treatment when symptoms appear and stops when symptoms get relieved, appears an effective strategy for maintenance therapy in GERD [56]. Apart from reduced cost of therapy, this will help in reducing the adverse effects associated with long-term continuous use of PPIs.

GERD: Extraesophageal symptoms and non-cardiac chest pain

GERD is the most frequent cause for non-cardiac chest pain (NCCP). Several extraesophageal symptoms are also associated with GERD. Important ones include laryngopharyngeal reflux (LPR), chronic cough, asthma, otitis media and dental erosion. PPIs are often prescribed for these conditions. Indiscriminate and prolonged use of acid suppressants for these conditions is probably an important contributor to the inappropriate use of PPIs.

Statement 6A: For patients having non-cardiac chest pain or extraesophageal symptoms of GERD, a PPI trial of up to 8 weeks can be instituted.

Level of evidence - low; conditional recommendation

Statement 6B: Patients not responding to therapeutic trial of PPIs require objective evaluation for the diagnosis of GERD.

Good clinical practice statement; strong recommendation

Non-cardiac chest pain (NCCP) NCCP is defined as the presence of retrosternal chest pain with negative cardiac evaluation [57]. As GERD is the most common cause for NCCP, an initial trial of high-dose PPIs (also known as the PPI test) is suggested [58]. This PPI test consists of 14 to 28 days of administration of standard dose of PPIs twice daily and is considered positive, when there is at least a 50% improvement in the intensity and frequency of chest pain [59]. In a meta-analysis by Cremonini et al., in which eight parallel and crossover studies were included, a PPI trial reduced the risk of persistent pain (pooled RR 0.54, 95% CI: 0.41–0.71). The PPI test showed high sensitivity (80%) and specificity (73%) and NNT was 3 (95% CI: 2–4) [60]. Due to its high sensitivity and specificity, the PPI therapeutic trial can avoid endoscopy and pH studies in nearly 80% of patients, making it a cost-effective approach. The optimal duration of the PPI test has been suggested to be two weeks (may be extended to four weeks), as patients with GERD-related NCCP have a higher positive PPI test during the second week when compared to those with non-GERD-related NCCP (81% vs. 27%) [61]. In those with relief of symptoms, standard-dose PPIs may be continued for up to eight weeks. Non-responders should be considered for the evaluation of other causes for NCCP.

Laryngopharyngeal reflux This is one of the most frequently diagnosed extraesophageal manifestations of GERD by otolaryngologists, but the objective evidence of GERD is noted in less than half the patients [62]. Findings of inflammation in the laryngeal region are frequent in asymptomatic subjects and therefore, LPR is probably overdiagnosed in many patients [63]. Ideally, all patients with extraesophageal symptom should have objective tests to confirm GERD, but this may not be practical in all settings. Confirmation of the diagnosis of GERD with endoscopy and/or 24-hour ambulatory pH study is invasive and expensive and the latter is not freely available. A short course of PPIs is less likely to be associated with significant adverse effects and hence, a trial of PPIs for extraesophageal symptoms may be cost-effective in resource-limited countries. For LPR, a meta-analysis found the benefit of PPIs in causing relief of symptoms, but no difference was noted on objective measures of healing of laryngeal lesions (reflux finding score) [64]. Response to treatment was defined as a greater than 50% reduction in laryngeal symptoms. This was assessed in 10 of the trials included in the meta-analysis and they reported a 15% higher response (95% CI, 1–30%) rate with PPIs. However, there was no significant difference in reflux finding score between the two groups (four trials). The evidence for dose and the duration of PPI for LPR is weak, but almost all trials have used standard dose of PPIs twice daily for eight to 12 weeks [35]. Hence, a standard dose of PPIs twice daily may be used in patients with LPR. In patients with response, therapy may be continued for up to three months for healing of laryngeal inflammation and then switched to on-demand therapy [65]. There are no published

RCTs on PPIs vs. placebo for LPR from India, but open label and uncontrolled studies have found PPIs to be effective in both symptom relief and healing of laryngeal lesions [66, 67].

Chronic cough and asthma GERD is presumed to be one of the causes for non-specific chronic cough. A Cochrane meta-analysis did not find conclusive evidence of benefit of PPIs in complete relief of chronic cough (OR 0.46; 95% CI 0.19 to 1.15) [68]. However PPIs have shown benefit in improving cough score [69, 70]. The RCTs on PPIs for chronic cough have generally used standard dose of PPIs twice daily for eight to 12 weeks [68]. A therapeutic trial of four to eight weeks of standard-dose PPIs twice daily may be considered after other causes for chronic cough such as bronchial asthma, posterior nasal drip, smoking and medications have been excluded. The PPIs should be stopped if there is no response after four to eight weeks [65]. GERD has also been associated with an increased risk of asthma compared to controls, but the trials with PPIs have shown limited to no benefit [71, 72].

Patients with NCCP or extraesophageal symptoms who do not respond to PPI therapy need an objective evaluation to confirm the presence of GERD. This would avoid prolonged use of PPIs and identify other causes responsible for the symptoms.

Dyspepsia

Dyspeptic symptoms are frequent in the community and are a common reason for consultation at all levels of healthcare. About 70% to 80% of patients do not have an underlying cause detected on investigations and are labeled as having "functional dyspepsia" [73]. The global prevalence of dyspepsia is estimated to range from 5% to 20% and in India to be around 10% to 15% [74, 75]. The most common medications prescribed for dyspeptic symptoms are acid suppressants, including PPIs. While the acid secretion in patients with functional dyspepsia is not significantly elevated, duodenal hypersensitivity to acid and abnormal duodenal acid clearance in functional dyspepsia may explain the benefit of acid suppression [73, 76]. Western guidelines recommend a test and treat strategy for *H. pylori* for dyspeptic symptoms but data from India do not support this strategy [77, 78].

Statement 7A: In patients with uninvestigated dyspepsia, without alarm symptoms, a standard-dose PPI should be used for 2 to 4 weeks as an initial therapy.

Level of evidence - moderate; strong recommendation

Statement 7B: In patients with functional dyspepsia, standard-dose PPIs should be used for 2 to 4 weeks as an initial therapy.

Level of evidence - moderate; strong recommendation

Statement 7C: In patients with uninvestigated dyspepsia without alarm features, prolonged or continuous use of PPIs is not recommended.

Good clinical practice statement; strong recommendation

Considering the prevalent nature of dyspepsia, there is a significant potential for inappropriate use and overuse of PPIs for this condition. PPIs lead to relief of symptoms in up to 70% of patients with dyspepsia [79]. A meta-analysis of six RCTs, including patients with dyspepsia, has shown PPIs to be superior to placebo [77]. Similar findings were also observed in a Cochrane meta-analysis, which was restricted to patients with "functional dyspepsia" [80]. A standard-dose PPI for two to four weeks is effective in treating dyspeptic symptoms in most patients. There has been no demonstrable benefit of high dose compared to standard dose and hence, standard dose of PPIs is recommended for these patients [77, 81]. Most of the RCTs have used PPI for two to eight weeks of therapy and PPI use beyond eight week is generally not recommended in patients with dyspepsia [82]. In those who respond to PPIs, the medication should be discontinued after completing therapy and subsequently used on demand if symptoms recur [77].

Patients with dyspepsia without alarm features and under 40 years of age do not require investigation with UGI endoscopy as the risk of malignancy is very low [83]. For uninvestigated dyspepsia, a therapeutic trial of PPIs for four to eighth weeks is appropriate [77]. If there is no response to therapy, PPIs should be discontinued and alternative therapy considered along with evaluation for organic causes and psychological factors [77].

Helicobacter pylori

Statement 8: Standard-dose PPIs in twice daily doses is an essential component of the drug therapy for the eradication of *H. pylori*.

Level of evidence - high; strong recommendation

The ISG has recently published its guidelines on *H. pylori* infection, which provides detailed information on the management of this infection [78]. PPIs enhance the effect of antibiotics and they are an integral component of *H. pylori* eradication therapy. The duration of therapy ranges from 10 to 14 days (14 days being preferred) [84]. PPIs twice daily is more effective than single daily dose. A standard dose of PPI is therefore given twice daily along with the antibiotics for the entire duration of therapy [85]. The newer PPIs (esomeprazole, rabeprazole) have been shown to be better than older ones in eradication rate, but the difference is quite small and hence, any PPI may be used [86].

Peptic ulcer disease

Statement 9: In patients with peptic ulcer disease, after *H. pylori* eradication therapy, PPI in standard dose should be given for additional 2 weeks for duodenal ulcer and at least 4 weeks for gastric ulcer.

Level of evidence - moderate; strong recommendation

Statement 10: After successful endoscopic therapy for bleeding peptic ulcer, high-dose PPI is recommended for 72 hours.

Level of evidence - high; strong recommendation

PPIs help in the healing of peptic ulcers by strong inhibition of gastric acid production. A majority (>90%) of duodenal ulcers heal after four weeks of standard-dose PPI therapy [87, 88]. Gastric ulcers, subject to the size of ulcer, may take up to six weeks of PPI therapy to heal [89, 90]. Standard *H. pylori* eradication regimen includes 14 days of double dose PPIs [78]. Hence, two more weeks of PPIs is recommended for duodenal ulcer and four more weeks for gastric ulcer to ensure healing of the lesion. NSAID is the second important cause of PUD and discontinuing this drug along with therapy with PPIs is recommended for ulcer healing. If NSAID cannot be stopped, then PPIs should be continued for as long as the patient is on NSAID [91].

PPI after endotherapy for bleeding ulcer PPI, by raising the intragastric pH, promote clot formation and stability and inhibit pepsin-induced clot lysis. In a recent meta-analysis of seven RCTs, after successful endoscopic intervention for bleeding peptic ulcer, high-dose PPI therapy reduced re-bleeding rates (RR = 0.43, 0.33–0.56), mortality (RR = 0.41, 0.22–0.79) and need for surgical intervention (RR = 0.42, 0.25–0.71) when compared to no treatment [92]. The NNT for preventing re-bleed, surgery and mortality were 10, 33 and 50, respectively. Two important RCTs are available from India on the utility of PPIs in peptic ulcer bleeding [93, 94]. Both studies reported a reduction in re-bleeding rates, requirement of number of blood transfusions and length of hospital stay with the use of PPIs. Neither of the studies showed an improvement in need for surgery and mortality with PPIs. PPIs are beneficial, even when initiated before the index endoscopy. They lead to downgrading of endoscopic stigmata of recent hemorrhage and reduce the need for endoscopic therapy [95]. There is evidence to suggest that intermittent dosing of PPIs may be as effective as intravenous bolus dose followed by continuous infusion for bleeding peptic ulcer. A systematic review and meta-analysis compared intravenous bolus followed by continuous infusion vs. intermittent dosing of PPIs for UGI bleed [96]. The outcomes of re-bleeding, blood transfusion requirement, need for reintervention and the length of hospital stay were comparable between the two groups [96]. An intermittent dosing strategy would require lower dose compared to continuous infusion and may be preferable in this setting. After the completion of high-dose intravenous PPIs for 72 hours, further therapy with oral PPI is given for four to six weeks for healing of the ulcer [97].

Eosinophilic esophagitis

Statement 11: In patients with eosinophilic esophagitis, PPIs, dietary elimination and topical glucocorticoid alone or in combination may be used as the first-line therapy.

Level of evidence - moderate; strong recommendation

After the AGREE (a working group on PPI responsive esophageal eosinophilia) conference in 2018, the mandatory eight-week PPI trial as diagnostic criteria for eosinophilic esophagitis (EOE) was removed in favor of placing these as a first-line therapeutic option along with dietary modifications and topical corticosteroids [98]. In a meta-analysis of 33 studies, including 619 patients with symptomatic esophageal eosinophilia, Lucendo et al. reported pooled clinical and histological response rate of 61% and 51%, respectively, with PPI therapy, although with high heterogeneity in response ($I^2 = 80.2$) [99]. In another meta-analysis, Rank et al. reported histologic response in 41.7% of patients with PPIs compared to 13.3% in the historical placebo group (RR, 0.66; 0.61–0.72) [100]. In view of their efficacy, safety profile and better compliance, PPIs may be considered among the initial therapies in patients with EOE for induction of remission [101, 102]. Follow-up after treatment is essential, as non-response would necessitate switching to other therapies.

Real-world practice data from two large studies reported better clinicopathologic remission rates with high dose of PPI [103, 104]. Available evidence does not favor any specific PPIs over others. Patients with predominant fibro stenotic phenotype and past failure to topical steroids may be less responsive to PPIs [104]. Further studies are needed to validate maintenance treatment protocols in terms of dose and duration. However, stepping down to the lowest effective dose to maintain remission appears to be preferable [105, 106].

PPI prophylaxis

Antiplatelet agents

Statement 12: Standard-dose PPI prophylaxis may be introduced in patients receiving single antiplatelet drug in the presence of additional risk factors or in those on dual antiplatelet drugs.

Level of evidence - moderate; strong recommendation

Antiplatelets are associated with risk of peptic ulcer and gastrointestinal bleed and assessing the need for administering PPI prophylaxis is important [107]. The risk of GI bleeding is 1.8 times (95% CI: 1.5–2.1) higher with low-dose aspirin, while addition of another antiplatelet agent can increase this risk to up to four times (95% CI: 3.5–5.15) [108]. A recent meta-analysis of six RCTs (6930 patients) showed that the use of PPIs significantly reduces the risk of any GI bleeding (RR 0.37; 0.24–0.58) and specifically upper GI bleeding (RR 0.40; 0.24–0.64) in patients treated with dual antiplatelet (DAPT) [109]. No clear association between PPI use and increase in risk of major adverse cardiovascular events (3 RCTs, RR 0.89; 0.75–1.05),

myocardial infarction (3 RCTs, RR 0.93; 0.76–1.15) or all-cause mortality (4 RCTs, RR 0.79; 0.50–1.23) was found. The presence of additional risk factors in this scenario may further increase the risk of GI bleeding [110–113]. Among the various risk factors reported, the strongest association has been seen with a past history of complicated peptic ulcer (RR 15.4; 12.6–18.9) [111]. Other risk factors include advanced age, concomitant use of anticoagulants, steroids and NSAIDs and *H. pylori* infection (Table 4) [113–118]. *H. pylori* infection should be tested for and, if present, eradicated [112].

Overall, the use of dual antiplatelet alone or single antiplatelet drug in the presence of additional risk factors increases the risk of GI bleeding and hence, PPI prophylaxis should be provided to such patients [112, 113].

Table 4 Additional risk factors for gastrointestinal bleeding in patients on antiplatelet therapy

Risk factor	Hazard ratio (95% CI)
Previous history of complicated peptic ulcer	15.4 (12.6–18.9)
Dual antiplatelet therapy	3.18 (1.91–5.29)
Concomitant NSAID use	1.88 (1.46–2.43)
Age (10 year increment)*	1.51 (1.21–1.90)
NYHA Class 3 or 4	2.27 (1.41–3.64)
Concomitant use of anticoagulant therapy	2.13 (1.28–3.52)
Concomitant use of steroids	1.43 (1.22–1.66)

*The increase in hazard ratio for every 10 years increase in age

NSAID nonsteroidal anti-inflammatory drug, *NYHA* New York Heart Association

Anticoagulants

Statement 13: For patients on anticoagulants, standard-dose PPI prophylaxis is recommended only if there are additional risk factors.

Level of evidence - low; strong recommendation

Anticoagulants (dicumarinics/vitamin K antagonists, e.g. warfarin; direct-acting oral anticoagulants (DOACs) including factor Xa inhibitors apixaban, edoxaban and rivaroxaban; and direct thrombin inhibitor, dabigatran) are used to prevent and treat venous thromboembolism and prevent arterial thromboembolism in patients at high risk for thrombotic or thromboembolic events [119–121]. These anticoagulants are not ulcerogenic, but can increase the risk of bleeding from pre-existing mucosal breaks. An exception to this is dabigatran, which has a direct topical anticoagulant effect as well. An increased risk of gastrointestinal (GI) bleeding with these agents can result in a significant morbidity and mortality and use of PPIs has been shown to decrease the risk of GI bleeding [120–123].

In a meta-analysis of six nested case-control or cohort studies, PPI use was protective against upper GI bleeding in patients on dicumarinics (RR, 0.56; 0.38 to 0.83) but not in patients on dabigatran (hazard ratio [HR], 0.78; 0.44 to 1.37) [124]. In a retrospective cohort study with a follow-up of 75,720 person-years of active warfarin therapy, the risk of hospitalization due to upper GI bleeding in all patients on warfarin (including those on antiplatelets and NSAIDs) was reduced by 24% (adjusted HR=0.76; 0.63 to 0.91) with the use of PPIs [125]. In patients who were on antiplatelet drugs or NSAIDs, the risk of GI bleed reduced by 45% (HR, 0.55; 0.39–0.77) with PPI co-therapy, while there was no protective effect for patients on warfarin alone. The same holds true for patients on non-vitamin K antagonist oral anticoagulants (NOACs) as shown by a cohort study, including 164,290 NOAC users with atrial fibrillation, with 39,938 years of PPI exposure and follow-up of 272,570 person-years [126]. Upper GI bleeding was noted in 806 patients and the protective effect of PPIs in the prevention of upper GI bleed was maximum in high-risk patients (those with age >75 years, HAS-BLED [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Age > 65 years, Drugs/alcohol concomitantly] score ≥ 3 and concomitant antiplatelet therapy) [127].

In a systematic review and meta-analysis of 10 studies, which included 1,970,931 patients, PPI co-treatment was related to lower odds of GI bleeding by 24% to 44% for all anticoagulants (except edoxaban) and this protective effect was more significant in patients with risk factors such as concurrent antiplatelets/NSAIDs, past GI bleed, HAS-BLED score ≥ 3 and underlying GI diseases [128].

A routine co-administration of PPIs with oral anticoagulants is therefore not warranted, especially because of a concern that PPI may increase serum warfarin concentration and increase the risk of GI bleeding as both these drugs are metabolized by similar cytochrome pathways. However, PPI co-therapy should be prescribed with vitamin K antagonists and DOACs, if there are co-existent major risk factors associated with GI bleeding which are summarized in Tables 5 and 6 [129–131].

Corticosteroids

Statement 14: In patients on short or long-term corticosteroids, routine PPI prophylaxis is not recommended.

Level of evidence - low; strong recommendation

The association between corticosteroids and PUD has been a source of debate. The results of earlier meta-analyses were mixed [132, 133]. A more recent meta-analysis of 159 double-blind RCTs (33,253 patients) has shown that corticosteroids slightly increase the risk of GI bleeding or perforation, only for the hospitalized patients (OR 1.43; 1.22 to 1.66) and not for ambulatory patients (OR 1.63; 0.42 to 6.34) [118]. Hence, the absolute risk appears to be low for

outpatients on corticosteroid therapy. Additionally, good-quality data showing PPI prophylaxis reduces this risk is generally lacking.

Patients on corticosteroids and concomitant NSAID intake or those admitted to hospital (especially critically ill patients) may be considered for PPI prophylaxis [118, 133–136]. *H. pylori* infection, if present, should be eradicated in such patients.

Nonsteroidal anti-inflammatory drugs

Statement 15A: Routine PPI prophylaxis is not recommended for all patients on nonsteroidal anti-inflammatory drugs.

Level of evidence -moderate; strong recommendation

Statement 15B: In patients taking NSAID, use of PPIs is recommended based on the risk assessment for the prevention of GI complications.

Good clinical practice statement; strong recommendation

NSAID-induced GI mucosal damage can result in ulcer formation in up to 25% of patients, but the risk of complication such as ulcer bleeding and perforation is lower (2% to 4%) with a relative risk of 3.8 (95% CI 3.6–4.1) [137–139]. PPIs are effective in healing NSAID-related GI mucosal damage [140–142]. In two multi-center RCTs, i.e. VENUS (844 patients, USA) and PLUTO (585 patients, multinational), the pooled ulcer rates were significantly reduced with the use of PPIs (16.5% on placebo, 0.9% on esomeprazole 20 mg; $p<0.001$ and 4.1% on esomeprazole 40 mg; $p=0.002$) [143, 5]. A recent Cochrane review (6 RCTs, 1259 patients) also showed that co-prescription of PPIs with NSAIDs reduced the risk of endoscopic duodenal ulcers (RR 0.20; 0.10 to 0.39) and gastric ulcers (RR 0.39; 0.31 to 0.50) when compared with placebo [144].

In a systematic review of 31 trials (> 12,500 participants), PPIs were more effective in reducing endoscopic ulcers (RR = 0.27; 0.22 to 0.33) and ulcer complications (RR = 0.29; 0.20 to 0.42) when compared to placebo. Interestingly, the NNT was 10 in high-risk for UGI bleeding patients, but was 268 in moderate-risk patients [91]. Therefore, prophylactic use of PPIs should be restricted to patients at high risk of GI bleed (Table 7). Among various risk factors for NSAID-induced GI bleeding, the most significant risk factor is the previous history of a complicated ulcer (OR 13.5) and concomitant use of NSAIDs and anticoagulants (Table 7). *H. pylori* is considered an independent risk factor and can increase the risk of peptic ulcer by six times in those on NSAIDs. Therefore, testing and treatment of infection should be done, ideally before starting long-term NSAIDs. There are reports that suggest an increased risk of small intestinal injury associated with PPI use in patients on NSAID or aspirin [145, 146]. A randomized study among patients on COX-2 inhibitors showed higher frequency of small bowel injury on follow-up capsule endoscopy (44.4% vs. 16.7%, $p=0.04$) [146]. A recent meta-analysis of 14 studies showed three times higher risk of small bowel injury with concomitant NSAID and PPI use compared to NSAID intake without PPIs [147]. This further emphasizes the need for cautious use of PPI prophylaxis with NSAIDs.

Table 5 Additional risk factors for gastrointestinal bleeding in patients receiving vitamin K antagonists

Risk factors	Relative risk (95% CI)
History of GI bleed	5.1 (1.9–13.5)
Cirrhosis of liver	6.9 (2.0–24.5)
NSAID	8.7 (7.3–10.4)
Aspirin	6.9 (5.9–8.28)
COX-2 inhibitors	5 (1.2–8.9)
Age >65 years	2.5 (1.2–5.5)
Mean INR >2.1	2.1 (1.0–4.2)

GI gastrointestinal, *INR* international normalized ratio, *NSAID* nonsteroidal anti-inflammatory drug

Table 6 Additional risk factors for gastrointestinal bleeding in patients receiving direct acting oral anticoagulants

Risk factors	OR (95% CI)
Age >75 years (dabigatran >70 years)	2.5(1.1–3.2)
History of peptic ulcer complicated by bleeding	OR 2.5 (1.3–4.7)
Concomitant use of aspirin or NSAIDs	OR 1.8 (1.01–8.9)
HAS-BLED score ≥3	Twice the risk compared to score <3

OR odds ratio, *HAS-BLED* Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Age > 65 years, Drugs/alcohol concomitantly, *NSAIDs* non-steroidal anti-inflammatory drugs

Stress ulcer prophylaxis

Statement 16: In critically ill patients, prophylaxis with standard-dose PPI is recommended only in the presence of risk factors for gastrointestinal bleeding.

Level of evidence - moderate; strong recommendation

Patients admitted with critical illness to the hospital are at the risk of developing stress ulcers. Though the occurrence of ulcer on upper GI endoscopy is frequent, overt bleeding has been observed in 1.5% to 8.5% of patients and only 1% to 3% of patients have a clinically significant bleeding (hypotension, tachycardia, requirement of blood transfusion, need for vasopressor therapy and drop in hemoglobin by > 2 g%) [148, 149]. Several risk factors (Table 8) for clinically significant bleeding have been described and the two most important ones are respiratory failure requiring mechanical ventilation (OR 15.6) and coagulopathy (OR 4.3) [150]. PPI prophylaxis is helpful in reducing the risk of clinically

Table 7 Additional risk factors for gastrointestinal bleeding in patients receiving non-steroidal anti-inflammatory drugs

Risk factor	Adjusted RR or OR (95% CI)
Previous complicated ulcer	15.4 (12.6–18.9)
Concomitant anticoagulant treatment	8.7 (7.3–10.4)
Concomitant multiple NSAIDs (including aspirin)	7.8 (5.2–11.7)
Concomitant high-dose NSAID	5.8 (4.0–8.6)
Previous uncomplicated ulcer	4.6 (1.9–11.0)
Age 70–80 years	4.3 (3.5–5.3)
H. pylori infection	3.5 (2.16–5.75)
Concomitant oral corticosteroids	2.4 (1.6–3.6)

NSAID non-steroidal anti-inflammatory drug, *OR* odds ratio, *RR* relative risk

significant bleeding and duration of stay in the intensive care unit, but its impact on reducing mortality is not well established. Two large meta-analyses have reported a reduction in risk of clinically significant bleeding of around 60%, when compared to placebo [151, 152].

In the absence of any of the reported risk factors, stress ulcer bleeding is uncommon [153, 154]. A couple of meta-analyses on PPI have raised concerns about an increased risk of infectious complications such as nosocomial pneumonia and *Clostridium difficile*–associated diarrhea, although other reports have refuted this [151, 155–157]. In patients with cirrhosis, stress ulcer prophylaxis with PPIs may increase the chance of infections and also the risk of morbidity and mortality [154].

Considering the low chance of significant bleeding in patients without risk factors and the increased risk of infection, PPI prophylaxis should be reserved for patients admitted to hospital with risk factors for significant bleeding (Table 8) [148, 158]. In other words, all patients admitted to intensive care unit and/or critically ill do not need PPI prophylaxis.

Post-endoscopic variceal ligation ulcer bleeding prophylaxis

Statement 17: Standard-dose PPI may be considered for short duration after endoscopic variceal ligation.

Level of evidence - low; statement not accepted, no recommendation

An ulcer formation as a consequence of endoscopic variceal ligation (EVL) is common, although bleeding from such ulcers is rare but potentially serious [159]. A recent meta-analysis, consisting of 11 studies, including four RCTs, has shown the beneficial effect of PPIs after endoscopic therapy for esophagogastric varices in preventing re-bleeding (OR 0.52; 0.35–0.77; p =0.001) [160]. This meta-analysis had moderate heterogeneity since it included studies on patients undergoing sclerotherapy for esophageal varices and glue therapy for gastric varices. Most re-bleed from post-EVL ulcers occur 13.5 ± 7.3 days (range of 2-29 days) after an EVL procedure. Therefore, PPIs, if used, should not be prescribed for more than two to three weeks [159].

On the other hand, there are safety concerns with the use of PPIs in patients with cirrhosis of liver (addressed in detail later). Additionally, the presence of other factors such as liver dysfunction, degree of portal hypertension and coagulation profile are relevant in predicting re-bleeding. Recent publications such as the Baveno VII consensus and European Society of Gastrointestinal Endoscopy (ESGE) guideline for the management of variceal hemorrhage have recommended against the continuation of PPI post-endoscopic therapy for variceal bleeding citing safety issues [161, 162]. Overall, the balance of risk-benefit of using PPI after EVL is unclear and the group was not able to make any specific recommendation.

PPIs in special situations

Chronic kidney disease

Statement 18: If indicated, PPIs in standard dose can be used in patients with chronic kidney disease.

Level of evidence - very low; strong recommendation

PPIs have been linked with various disorders of the kidney, including acute interstitial nephritis and chronic kidney disease (CKD). In a retrospective analysis of data from 178,228 patients, the exposure to PPIs was higher in those having CKD stages 3-4 than in those having no CKD [163]. The higher prevalence of CKD in them may be secondary to the higher incidence of acid-related gastrointestinal disorders

Table 8 Risk factors for significant bleeding from stress ulcers in critically ill patients

Risk factors
• Coagulopathy (abnormal PT or PTT or thrombocytopenia)
• Mechanical ventilation
• Previous history of upper gastrointestinal bleeding
• Major burn
• Acute traumatic brain or spinal cord injury
• Patients with 2 of the following three—sepsis, ICU stay longer than one week, receiving high-dose steroids
• Multiple trauma
• Use of antiplatelet or non-steroidal anti-inflammatory agents
• Renal failure or renal replacement therapy
• Liver failure
• Liver or renal transplantation

Source: Reference [154]

ICU intensive care unit, *PT* prothrombin time, *PTT* partial thromboplastin time

from hypergastrinemia, reduced mucosal prostaglandins and co-prescription of medications such as antiplatelet agents in patients with CKD [163, 164]. The literature on the safety of PPI use in patients with already established CKD is limited and has shown conflicting results. Grant et al. reported an increased risk of major kidney adverse events, defined as doubling of serum creatinine or progression to end-stage renal disease, in those with PPI use (55.5% vs. 36.6%, $p < 0.001$; OR 1.13; 1.02 to 1.25), but without an increase in the risk of mortality [165]. Subsequently, Cholin et al. using a retrospective analysis of a large cohort of patients did not observe any difference in the incidence rates of progression to end-stage kidney disease (ESKD) and overall mortality among those with PPI use and those without [166]. Another prospective cohort analysis reported an increased adjusted risk for ESKD with PPI use than those without (HR 1.74; 1.26–2.40) [167]. Overall, the current evidence on the risk of PPI in accelerating progression of CKD is conflicting. Hence, PPIs may be used in patients with CKD in the presence of a proper indication, but indiscriminate use must be avoided.

Cirrhosis of liver

Statement 19: In patients with cirrhosis of the liver, PPIs should be used with caution.

Level of evidence - very low; strong recommendation

PPIs are used frequently in patients with cirrhosis of the liver and often without a proper indication [168, 169]. Data from multiple studies and several meta-analysis have shown an increased risk of various adverse outcomes in cirrhotic patients on PPI [170–175]. A recent meta-analysis of 47 studies, including patients with both compensated and decompensated cirrhosis, reported a constellation of adverse outcomes related to the long-term use of PPIs in them. The pooled OR for hepatic encephalopathy, spontaneous bacterial peritonitis, bacterial infections and mortality in PPI users compared to non-users was 2.31 (95% CI 1.63–3.28), 1.72 (95% CI 1.42–2.09), 1.76 (95% CI 1.52–2.03) and 1.29 (95% CI 1.11–1.49), respectively [176]. Many of the studies had limitations such as retrospective design and presence of confounding factor(s) [177]. Some of the adverse effects in the individual studies were found to be dose dependent [178, 179].

Hence, there is a need for restricted use of PPIs in patients with cirrhosis of the liver and if indicated, they should be used only for a brief period [180]. Furthermore, PPIs are generally metabolized in the liver and in patients with decompensated liver disease, their metabolism may be affected [181]. A comprehensive review on PPIs in chronic liver disease favored use of rabeprazole, omeprazole or esomeprazole for CTP (Child-Turcotte-Pugh) A or B disease and esomeprazole (20 mg) for CTP C cirrhosis [181].

Chronic pancreatitis

Statement 20: In patients receiving pancreatic enzyme therapy, routine use of PPIs is not recommended.

Level of evidence - low; strong recommendation

Pancreatic enzyme replacement therapy (PERT) is safe and effective for treating pancreatic exocrine insufficiency in patients with chronic pancreatitis (CP) [182, 183]. Commonly available enteric-coated preparations of PERT require duodenal pH of 5.5 or greater for optimum efficacy. Use of PPIs to increase pH may be potentially beneficial, but evidence to support the routine use of PPIs with PERT is generally lacking [184–188]. Sander-Struckmeier et al. integrated data from all clinical trials with use of pancrelipase/pancreatin (34 trials, 1142 unique subjects) and assessed the role of PPI/H_2RA in improving absorption of fat. They observed no differences in mean coefficient of fat absorption values at the end of treatment irrespective of disease type (cystic fibrosis, chronic pancreatitis and pancreatic surgery) between the group receiving PPI/H_2RA and not receiving acid suppression [187]. Hence, routine use of PPIs for patients with chronic pancreatitis receiving PERT is not recommended. The use of PPIs should be reserved for those showing sub-optimal response to PERT despite using adequate dose of enzyme supplements.

Pancreatic enzymes are also used for pain relief in patients with chronic pancreatitis although the evidence to support this is generally lacking [189–191]. There is some evidence supporting the use of non-enteric-coated pancreatic enzymes for relieving pain in patients with chronic pancreatitis [192]. Non-enteric-coated preparations release their contents within duodenum-proximal small intestine and may offer more effective feedback inhibition of pancreatic secretion. Since acid environment in the stomach may hamper the efficacy of non-enteric-coated pancreatic enzymes, PPIs may help in decreasing the gastric pH. However, the beneficial effect of PPIs in this setting needs to be demonstrated further.

Pediatric population

Statement 21A: PPIs are indicated in children over 1 year of age for a short-term for the treatment of symptomatic GERD, healing of erosive esophagitis, peptic ulcer disease and *H. pylori* eradication.

Level of evidence - low; strong recommendation

Statement 21B: Use of PPIs should be discouraged in children below 1 year of age.

Good clinical practice statement; strong recommendation

Infants and younger children require relatively higher per-kilogram dose of PPIs to achieve similar acid suppression than adults, as they appear to metabolize PPI more rapidly. The pediatric dose in general, however, should not exceed the higher end of dose

used in adults [193, 194]. The RCTs in children, above one year of age, have shown that PPIs are effective in treatment of GERD especially erosive esophagitis [195–198]. They are well tolerated and have superior efficacy than H_2RA [199]. Most pediatric guidelines recommend the use of four to eight weeks of PPIs in children having typical GERD symptoms [200–202]. Evidence to support empirical PPI trial for the diagnosis of extraesophageal symptoms of GERD is generally lacking in children [200, 201]. Furthermore, PPIs are an essential component of *H. pylori* eradication regimens in children similar to that in adult and also the drug of choice for treating peptic ulcer disease [203]. Their role in eosinophilic esophagitis has been discussed earlier (Statement 11).

Data from different parts of the world has depicted a significant rise in the prescription of PPIs in infants [204, 205]. However, evidence is lacking to support their use beyond the management of erosive esophagitis or acid reflux symptom [204, 206–208]. Furthermore, the dose-related effects of PPIs have not been validated appropriately in newborns and certain enzymes involved in their clearance take five to six months to attain maturation of activity [194, 205]. Recommendations from various society guidelines are consistent with the available evidence that PPIs are not effective for symptoms usually attributed to GERD in otherwise healthy infants such as sleep disturbance, irritability or unexplained crying [200, 201, 204]. Gastroesophageal reflux is physiological in most infants and tends to resolve over six to 12 months [200, 207]. Esomeprazole is the only PPI approved for use in infants after one month of age [207]. The daily dose of esomeprazole is based on the weight of infant: 3 to 5 kg—2.5 mg; 5 to 7.5 kg—5 mg; >7.5 kg—10 mg [201, 209].

Pregnancy

Statement 22A: A standard-dose PPI, if indicated, may be used in pregnant women in their second or third trimester of pregnancy.

Level of evidence - low; strong recommendation

Statement 22B: The use of PPIs should be avoided, unless there is a strong indication, during the first trimester of pregnancy.

Good clinical practice statement; strong recommendation

Gastrointestinal symptoms are common during pregnancy. A recent population-based nationwide study, which included 6,365,471 pregnancies in France between 2010 and 2018, showed doubling of PPI prescription rate in them during the study period [210]. Two meta-analysis (RR = 1.18; 0.72–1.94, 5 studies; RR = 1.12; 0.86–1.45, 7 studies) and a large database cohort study did not show significant added risk with the use of PPIs in pregnancy [165, 211–213]. However, more recent evidence has raised concerns regarding their safety in pregnancy. A meta-analysis, including 26 observational studies, reported an increased risk of congenital malformations with PPI use (OR 1.28; 1.09–1.52), especially in case-control studies (OR 2.04, 1.46-2.86) [214]. There were certain methodological limitations in these studies, both highlighted by the authors and Letter to Editor, which should be considered before interpretation of the results [214–216]. Lai et al., in the analysis of eight population-based studies, reported an increase in the overall risk of childhood asthma in children of PPI-using women during pregnancy (RR = 1.34; 1.18–1.52) [217].

Although the timing of exposure to PPI during pregnancy is not clearly defined in many studies, most drug safety studies during pregnancy have focused on congenital malformation, which occurs during the critical organ-forming phase of the first trimester [214]. Hence, PPIs may be used for appropriate indications during the second and third trimester of pregnancy, but use in first trimester should be restricted to only well-described indications, where benefits outweigh risk and no alternative treatment options are available [218].

Co-prescription of PPIs with other drugs

Prokinetics

Statement 23A: Routine addition of prokinetic to PPIs is not indicated in patients with GERD.

Level of evidence - moderate; strong recommendation

Statement 23B: Routine use of fixed dose combination therapy of PPIs and prokinetics should be avoided.

Good clinical practice statement; strong recommendation

Prokinetics are often used in combination with PPIs for the treatment of GERD. They increase lower esophageal sphincter (LES) pressure, enhance peristalsis and augment gastric emptying, which may benefit GERD patients [219]. However, evidence to support the routine use of such combination is not well established. A meta-analysis on the efficacy of combination therapy, including 12 RCTs (n=2403), reported no significant effect of prokinetics on symptom response or endoscopic mucosal healing (95% CI: 1.0–1.2, p = 0.05; 95% CI: 0.66–2.61, p = 0.44). A higher risk of adverse effects was observed in those, who received the combination therapy (95% CI: 1.06–1.36, p = 0.005) [220]. Another meta-analysis on the efficacy of the combination therapy reported 18% higher symptomatic improvement with combination therapy (pooled RR = 1.185; 1.042–1.348; p = 0.010), but no significant effect on mucosal healing (RR = 0.996; 0.929–1.068, p = 0.917) [221]. Interpretation of the above mentioned meta-analysis is limited in view of significant heterogeneity among the studies with regard to the type, dose and duration of prokinetics in the included studies and use of non-uniform methods for the assessment of the primary outcome measures.

Prokinetics may be used as an adjunctive therapy to PPI in cases with dysmotility-like symptoms and inadequate response to PPI. The American College of Gastroenterology and the ISG guidelines do not recommend the use of prokinetics routinely in patients with GERD in the absence of objective evidence of gastroparesis [27, 35, 222]. Furthermore, guidelines for the management of GERD in children also do not recommend prokinetics in otherwise healthy children with isolated overt regurgitation [223].

Antibiotics

Statement 24: There is no need to co-prescribe PPIs routinely in patients in whom antibiotics are prescribed.

Level of evidence - low; strong recommendation

There is no clinical rationale for co-prescribing PPIs routinely while prescribing antibiotics. An exception to this is *Helicobacter pylori* eradication therapy, where the use of PPIs in combination with antibiotics is essential. Combining antibiotics with PPIs may be associated with a heightened risk of adverse effects, especially *Clostridiodes difficile* infection (CDI)-related diarrhea [224]. This risk has been demonstrated both in animal and human studies [224–226]. Antibiotics and PPIs are known to cause alterations in the gut microbiota and hence, a combination of these two may increase the risk of CDI even further. A nationwide population-based cohort study from South Korea demonstrated higher risk of developing CDI-associated diarrhea with the use of PPIs among those who had used high-risk antibiotics [224].

Probiotics

Statement 25: There is no rationale for co-prescribing PPIs with probiotics routinely.

Level of evidence - moderate; strong recommendation

The proposed rationale of using probiotics and PPIs together is two-folds. While on the one hand, PPI, by reducing gastric acid, may improve the colonization by probiotic strains and enhance the efficacy of probiotics, the use of probiotics on the other may be potentially helpful in reducing the small intestinal bacterial overgrowth (SIBO) associated with PPI use. Hence, PPIs may improve the efficacy of probiotics and probiotics may reduce bacterial overgrowth-related adverse effect of PPI. Short-term PPI use has been shown to improve microbial abundance and the use of a multi-strain probiotic reduced the PPI-induced changes in healthy adults [227]. However, this trial and other studies have not explored any clinically relevant outcomes in the diseased populations to support the routine use of probiotics [227].

In a randomized study in pediatric patients, a combination of probiotic strain (*Lactobacillus reuteri* strain) with PPIs showed a reduction in the occurrence of SIBO as measured by breath test and also symptomatic SIBO [228]. In contrast, another randomized trial in pediatric patients receiving omeprazole did not show any benefit of probiotic (*Lactobacillus rhamnosus* and *Lactobacillus acidophilus* strains) in reducing the incidence of SIBO in them while on PPIs [229]. Therefore, at present there is no evidence for using PPIs for enhancing the efficacy of probiotics or vice versa.

Selective serotonin reuptake inhibitor

Statement 26: There is no indication for adding PPIs to SSRI routinely.

Level of evidence - low; strong recommendation

Selective serotonin reuptake inhibitor (SSRI) has been associated with an increased risk of GI bleeding [230, 231]. Mechanistically, it is suggested that the optimal platelet function requires serotonin and SSRI may impact the platelet function [232]. However, it is also believed that the initial action of SSRIs is pro-thrombotic, as they may induce platelet adhesion by their action on the 5-HT2 receptors. A systematic review of 32 studies suggested that among those on antiplatelets or anticoagulants, the users of SSRI and serotonin and norepinephrine reuptake inhibitor had higher odds of major bleeding, including GI bleeding, as compared to non-users [233]. The bleeding risk is deemed higher in those with underlying renal dysfunction and with concomitant use of NSAIDs [234, 235].

The benefit of PPIs in reducing the risk of bleeding in patients taking SSRIs was assessed in a meta-analysis [236]. The use of SSRI was associated with an increased risk of GI bleeding although the number needed to harm (NNH) was 1 in 791 for the general population. The NNH was 1 in 290 with concomitant antiplatelet use and 1 in 190 with concomitant NSAID use. Co-prescription of acid-suppressing drugs helped in reducing the risk of bleeding only in patients where SSRI and NSAIDs were co-prescribed, but not when SSRI was used alone [236]. The NNH was found to be even higher in another systematic review of 19 studies, i.e. 3177 and 881 in the low and high-risk populations, respectively [235]. Most of the published evidence suggests that the overall risk of bleeding is low and PPI prophylaxis may be relevant only in high-risk populations, e.g. elderly and those on NSAIDs [231, 237–239].

Furthermore, SSRI and PPIs have significant drug interactions; a 50% dose reduction is desirable for escitalopram if it is used with omeprazole or esomeprazole [240]. This is because the SSRIs are metabolized by CYP2C19, which is inhibited by PPIs. In patients on hemodialysis, the combined use of citalopram/escitalopram with PPIs has been associated with an increased mortality risk [241]. Considering these undesirable effects and the low absolute risk of GI bleeding, the decision to use PPI/antisecretory agents needs

to be individualized in patients who are on multiple drugs (SSRI with NSAIDs/antiplatelets/anticoagulants) or have co-morbidities.

Bisphosphonates

Statement 27: PPIs should not be routinely added while prescribing bisphosphonate.

Level of evidence - low; strong recommendation

There is evidence from animal studies that bisphosphonates cause gastric mucosal injury and may predispose to ulcer formation and delay healing of ulcers [242]. Evidence from human studies also suggests that bisphosphonates can cause gastric injury [243]. Therefore, PPIs are often combined with bisphosphonates in the belief that the combination may reduce esophagitis and gastric injury due to bisphosphonates. In an endoscopic study, the mean gastric injury scores were not different in individuals receiving gastric protected or usual alendronate 70 mg/day (much higher than clinically used dose), but were higher than in placebo, suggesting that bisphosphonates do cause some gastric injury at a high dose [244] In a 14-day study at approved doses, the incidence of gastric ulcers with risedronate was 6% as compared to 12% in alendronate arm suggesting that the use of bisphosphonates may be associated with the risk of gastric ulcers independent of *H. pylori* [245]. However, in a large retrospective study using a claims database, gastrointestinal events occurred in around a quarter of patients and were common irrespective of bisphosphonate use [246].

An RCT suggested that combining rabeprazole with risedronate may improve physical conditioning and bone mineral density more than risedronate alone, but this trial did not address the risk of gastrointestinal adverse effects, including ulcer healing [247]. A meta-analysis of four studies suggested that there may be an increased risk of fractures with the combined use of bisphosphonates and PPIs [248]. In view of contrasting evidence regarding the effect on bone health and lack of evidence vis-a-vis the protective effect of PPIs concerning the prevention of GI adverse effects of bisphosphonates, we do not suggest routine co-prescription of PPIs. However, in the presence of additional risk factors such as concomitant NSAID intake and previous GI bleed, it may be important to address risk factors (including *H. pylori*) and decide on the use of PPIs on a case-to-case basis.

Adverse effects of PPI

Statement 28: Use of PPIs is associated with an increased risk of certain gastrointestinal infections.

Level of evidence - low

The use of PPIs could potentially increase the risk of enteric infections due to strong inhibition of acid secretion. A meta-analysis of nine studies showed the use of PPIs to be associated with a higher risk of community-acquired enteric infections (pooled OR 4.28; 3.01–6.08). The association was especially strong for infections by *Salmonella* and *Campylobacter* [249]. An earlier systematic review had demonstrated that such a risk was present with all antisecretory therapies, but the risk was higher with the use of PPIs than with H_2RA blockers. The reported duration of use of PPIs in various studies was variable from one week to one year, but most studies evaluated PPI use in the previous month before infection [250].

A higher risk of CDI has also been noted with the use of PPIs, although the strength of association is not as strong as that for *Salmonella infection* [250]. PPI use has been reported to cause dysbiosis which perhaps increases the risk of CDI [251, 252]. In a meta-analysis of 50 studies reporting on the risk of CDI with PPI use, the pooled odds were higher in PPI users than in non-users (OR: 1.26; 1.12–1.39). The risk seemed to be significantly higher for hospital-acquired CDI but not for community-acquired CDI [253]. In addition, the odds of recurrence of CDI is also higher among PPI users than in non-users (1.84; 1.18–2.85) as shown in a systematic review of nine studies, which included 5668 patients [254].

There have been some reports that PPI use impacts the clinical outcomes of Coronavirus diseae - 19 (Covid-19) infection. A systematic review of 12 studies suggested that PPI use is associated with worsened outcomes, including mortality or severe Covid-19 (OR 1.85; 1.13–3.03). However, the use of PPIs did not increase the susceptibility to the acquisition of Covid-19 infection [255]. Another systematic review also had similar conclusions [256]. The use of PPIs is also associated with an increased risk of SIBO [257, 258]. The flora in SIBO may be variable and using PPI may predispose to gram-positive flora [257]. In a systematic review of 11 studies, including 3134 individuals, the use of PPIs was associated with increased pooled OR of SIBO (2.282, 1.238–4.205) [259].

The quantum of available evidence clearly shows an increased risk of GI infection with PPI use and hence, use of PPIs should be avoided in the absence of a definitive indication.

Statement 29: Use of PPIs is associated with increase in the risk of acute interstitial nephritis.

Level of evidence - low

The incidence of acute kidney injury in the community not requiring dialysis is estimated to be around 384 per 100,000 person-years (24.4 per 100,000 year for dialysis requiring acute kidney injury). Use of PPIs has been associated with the risk of kidney injury [260–264]. The mechanism of occurrence of CKD is unclear, but is believed to be due to the progression of acute interstitial nephritis (AIN). PPI-associated AIN is a subtle disease without significant systemic features and may remain unrecognized [265]. In a report of 64 patients with PPI-associated AIN, the mean time to onset after PPI use was around 13 weeks [261]. The risk seems to

be higher in elderly although the overall risk may be small (0.32 vs. 0.11/1000 person-years in controls) [266]. Because of the small risk of AIN, routine monitoring of all patients, while on PPI, may not be cost-effective.

In a systematic review of nine studies, the use of PPIs was associated with an increased risk of CKD, ESRD, acute interstitial nephritis and acute kidney injury. The risk was highest for acute interstitial nephritis [260]. Another systematic review, including seven studies suggested an increased risk (RR: 1.61; 1.16–2.22) of acute kidney injury in PPI users compared to non-users [262].

Statement 30: There is uncertainty about the increased risk of bone fracture with use of PPIs.

Level of evidence - very low

One of the concerning adverse effects of PPIs has been a higher risk of bone disease or fractures. The defects in mineral absorption with PPIs may contribute to this, but the published literature provides conflicting evidence regarding the risk of bone fractures. In a systematic review, which included 16 studies, the use of PPIs (short-term or long-term) was associated with increased risk of hip fractures (RR=1.26; 1.16–1.36), spinal fractures (RR=1.58; 1.38–1.82) and all-site fracture (RR=1.33; 1.15–1.54) [267]. A later systematic review of 24 studies also showed a higher risk of hip fracture with PPIs, the risk being higher with higher doses of PPIs [268]. Interestingly in a recent meta-analysis of six studies involving children and young adults, a higher risk of fracture with PPIs was also observed in this young population [269]. Another systematic review suggested that the increased risk of fractures was present irrespective of the duration (<1 or >1 year) of PPI use [270].

However, a Norwegian study (HUNT study) including 28,258 patients did not demonstrate an increased risk of fractures in PPI users [271]. In a randomized trial comparing pantoprazole vs. placebo in patients with stable cardiovascular or peripheral vascular disease, the use of pantoprazole was not found to increase the risk of fractures over a median follow-up of 3.01 years [272].

Therefore, there is uncertainty over the increase in the risk of bone fracture with PPI use. Furthermore, there is no evidence that screening and treatment of osteoporosis (with calcium, vitamin D or bisphosphonates) should be done prior to initiation of PPIs. Hence, the practical strategy for reducing the risk of fractures is to avoid the use of PPIs for inappropriate indications and avoiding prolonged usage unless clearly indicated.

Statement 31 A: Use of PPIs is associated with an increased risk of hypomagnesemia.

Level of evidence - low

Use of PPIs is associated with an increased risk of hypomagnesemia. This effect is possibly related to the inhibition of intestinal magnesium absorption by PPIs. The activity of the proteins involved in magnesium absorption from the intestine (i.e. transient receptor potential melastatin 6 and P7) is affected by the intraluminal acid-base balance [273]. Multiple meta-analyses have examined the effect of PPIs on magnesium levels and have demonstrated a dose-response effect [274, 275]. In a systematic review of 12 studies, the risk of hypomagnesemia among PPI user had a pooled adjusted OR of 1.71 (95% CI 1.33–2.19) as compared to non-users [274]. However, due to the high heterogeneity of the pooled estimates and lack of clarity about the frequency of clinically relevant hypomagnesemia, there is insufficient literature to recommend routine screening for magnesium levels at the start or during PPI therapy. In certain individuals with additional risk factors for hypomagnesemia, screening may be considered on a case-to-case basis such as critically ill patients and those receiving diuretics, digoxin or likely to receive long-term PPIs (> 1 year) [276–278].

Statement 31B: Long-term use of PPIs is associated with a small increase in risk of vitamin B_{12} and iron deficiency.

Level of evidence - low for vitamin B_{12} deficiency and very low for iron deficiency

Inhibition of acid production in the stomach due to use of PPIs may result in decrease in the absorption of certain nutrients. Vitamin B_{12} absorption is dependent on acid-dependent separation of B_{12} from a protein-bound form [279]. A systematic review of four studies suggested an increased hazard of developing B_{12} deficiency in patients with long-term acid-lowering therapy [280]. A recent systematic review of 25 studies found a higher risk of vitamin B_{12} deficiency among PPI users (OR 1.42; 1.16–1.73) [281]. Most studies included in this systematic review had reported PPI use of > 1 years. The risk may be more pronounced in the presence of additional risk factors such as vegan diet or concomitant use of drugs such as metformin [282].

The absorption of non-heme iron is believed to be related to gastric acidity. Achlorhydric state has been associated with iron deficiency [283]. The clinical evidence with respect to the effect of PPIs on iron absorption is, however, conflicting. In a study, including iron-deficient individuals, the omeprazole use was associated with reduction in iron absorption [284]. However, another study on long-term PPI use did not demonstrate any changes in iron profile and the authors suggested that iron monitoring is not warranted in those who are receiving PPIs [285]. Interestingly, a study reported that the use of PPIs could increase hepcidin production in HepG2 cell line and in mice [286]. A systematic review of nine studies found a higher risk of iron deficiency with the use of PPIs [287].

Due to inconsistence observations, we do not recommend routine monitoring of iron profiles during short-term use of PPIs. With long-term users, a decision to monitor or test for iron deficiency may be taken on a case-to-case basis.

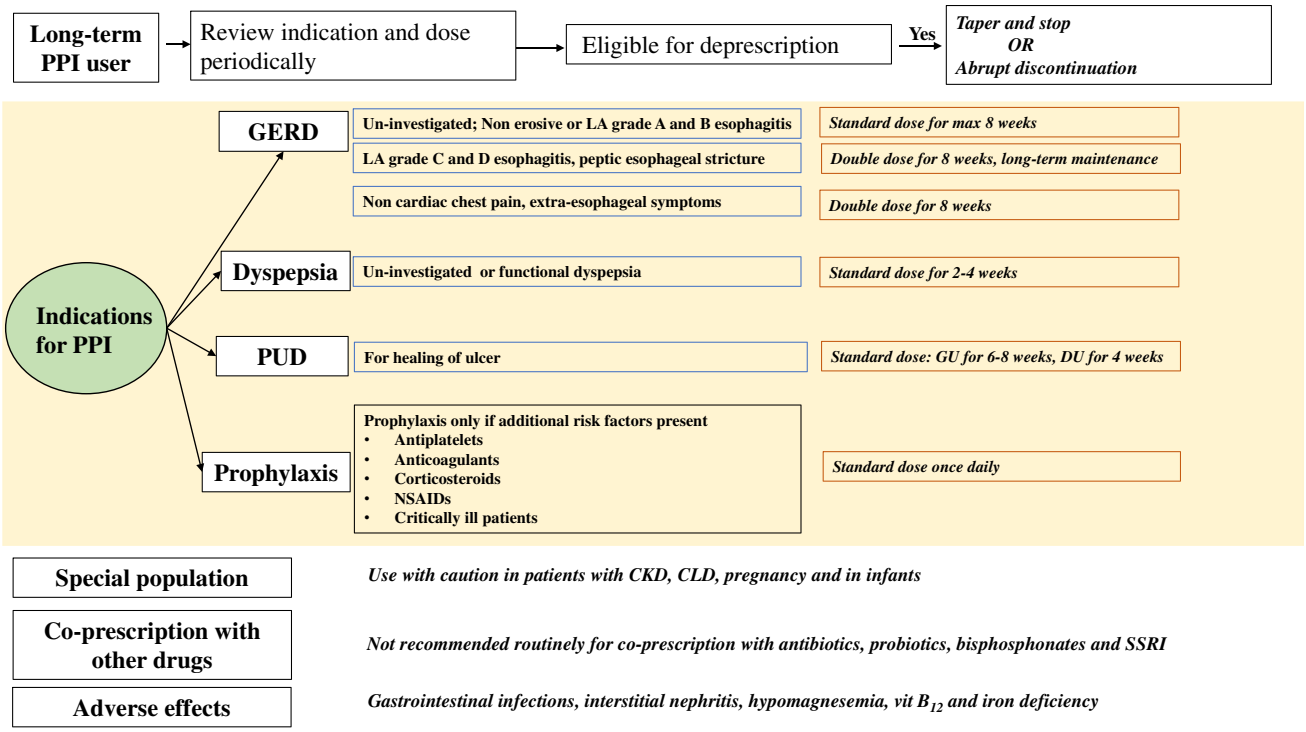

Fig. 1 Summary of key recommendations on rational use of proton pump inhibitors (PPI). *CKD* chronic kidney disease, *CLD* chronic liver disease, *DU* duodenal ulcer, *GERD* gastroesophageal reflux disease, *GU* gastric ulcer, *LA* Los Angeles, *NSAID* nonsteroidal anti-inflammatory drug, *PUD* peptic ulcer disease, *SSRI* selective serotonin reuptake inhibitors

Additional risks associated with PPIs

The effect of PPIs on the absorption of calcium is not clear [283]. The evidence regarding calcium absorption with short-term PPI use is conflicting. Some reports suggest that short-term PPIs may not be associated with reduced calcium absorption [288, 289]. Others have, on the contrary, suggested that PPI use inhibits calcium absorption [290–292]. In view of the conflicting evidence and also lack of population-level estimates regarding the frequency of symptomatic hypocalcemia, we do not suggest routine measurements of calcium levels before PPI initiation.

In a recent systematic review of 17 studies, the use of PPIs was not associated with an increased hazard of dementia (HR = 0.98; 0.85–1.13). This is in line with several other systematic reviews [293, 294]. Also, their use is not associated with an increase in the risk of Alzheimer's disease [294].

The suppression of gastric acid by the use of PPIs is also believed to predispose to community-acquired pneumonia. In a recent meta-analysis, including 13 studies, PPI use modestly increased the odds of community-acquired pneumonia (OR = 1.37; 1.22–1.53) [295]. This increased the risk of community-acquired pneumonia, which was also reported by previous multiple meta-analyses. These meta-analyses observed the risk of community-acquired pneumonia to be higher with current and recent PPI use, but not with the history of past PPI use [296, 297]. The risk is probably maximum with short-term use [295].

PPI use has also been implicated as risk factor for pancreatic, gastric, colorectal and liver cancer, but these associations are generally not very strong and it is difficult to draw firm conclusions [298, 299]. However, these observations further support judicious use of PPIs.

In conclusion, PPIs are used for a variety of indications and inappropriate use of PPIs remains an important concern. In this guideline, we have discussed and made recommendations for the appropriate indications as well as the duration of use of PPIs to promote its rational use (Fig. 1). The adverse effects have also been highlighted. We hope this will promote PPI stewardship in clinical practice.

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discussion/voting on evidence for statements and recommendation, manuscript writing. **Members:** U C Ghoshal, U Dutta, V Jayanthi, V Ahuja, S P Singh, A Kumar, N Bhat, S Nijhawan, U Poddar, G N Ramesh, Ajay Jain, S Zargar, N Berry, U Jalihal. Contribution—discussion/voting on evidence for statements and recommendation, manuscript review and editing.

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